

MEDICAL REVIEW OF SAFETY AND EFFICACY  
CONCLUSIONS

NDA #: 21,290

Sponsor: Actelion

Drug Name: bosentan

Type of Document: new drug application

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Medical Reviewer: Maryann Gordon, M.D.

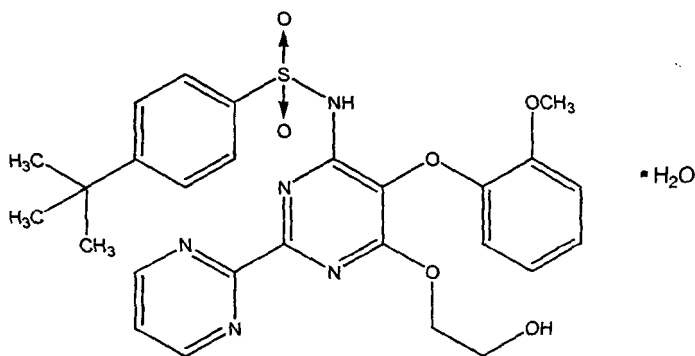
General Information:

Name of Drug

Generic: bosentan

Trade: Tracleer™

Structural Formula:



Pharmacological Category: endothelin receptor antagonist

Proposed Indication: treatment of pulmonary arterial hypertension

Dosage Form: 62.5 mg and 125 mg tablets

Route of Administration: oral

**Summary**

**Benefits**

Bosentan has been evaluated for efficacy in pulmonary arterial hypertension (PAH) in 3 studies, 2 with the oral formulation evaluating walking distance and 1 with the iv formulation evaluating acute hemodynamics. The latter trial was stopped prematurely for safety reasons and is included in the full efficacy review only for completeness.

Study no.	Design/duration	Primary efficacy parameter	No. planned/completed	doses	Patient types
AC 052-352	Double blind, randomized, placebo controlled for 16 weeks	6 min walk test	150/214	Oral 62.5 mg bid up titrated to 125 mg bid; 62.5 mg bid up titrated to 250 mg bid	-with PAH resulting from primary pulmonary hypertension or connective tissue or autoimmune disease; -WHO functional class III-IV despite optimal therapy with vasodilators, cardiac glycosides, diuretics, and /or supplemental oxygen; -receiving anticoagulants -neither receiving nor scheduled to receive epoprostenol (Flolan); -can walk between 150 m and 500 m, inclusive, on a 6-minute walk test. (reduced to 450 m for 352)
AC 052-351	Double blind, randomized, placebo controlled for 12 weeks	6 min walk test	30/32	Oral 62.5 mg bid up titrated to 125 mg bid at week 4	Same as above

### 6 minute walking distance

Bosentan, compared to placebo significantly increased mean walking distance in both study AC 052 352 (352) and study AC 052 351 (351).

Mean distances  $\pm$  SD (m)

	Study 352			Study 351	
	Bos 125 mg bid N=74	Bos 250 mg bid=70	Placebo bid N=69	Bos 125 mg bid N=21	Placebo bid N=11
Baseline	326 $\pm$ 73	333 $\pm$ 75	344 $\pm$ 76	360 $\pm$ 86	355 $\pm$ 82
Endpoint <sup>^</sup>	353 $\pm$ 115	380 $\pm$ 101	336 $\pm$ 130	430 $\pm$ 66	350 $\pm$ 147
Change from baseline	27 $\pm$ 75	46 $\pm$ 62	-8 $\pm$ 96	70 $\pm$ 56	-6 $\pm$ 120
Placebo subtracted effect	35***	54***	-	76*	-

<sup>^</sup> week 16 for study 352, week 12 for study 351

\*p=0.020 using Student's t-test

\*\*\* p=0.0002 for combined bosentan effect using Wilcoxon test.

### Dose effect

Only study 352 used more than 1 dose of bosentan in a parallel group design. In this study, the 250 mg bid bosentan group was numerically superior in walking distance to the 125 mg bid group at weeks 8 and 16, but there was overlapping of confidence limits at both time points. Although 62.5 mg bid was the starting dose for both studies, it was never adequately evaluated for efficacy.

### Walk distance by visit

In both studies, after an initial increase from baseline (at week 4), the placebo groups walking distance was similar to their baseline distance. The bosentan groups, on the other hand, had an increase in walking distance that was maintained for 12 and 16 weeks.

### **Secondary endpoints**

Time to clinical worsening was defined as the shortest time to death, lung transplantation, hospitalization or discontinuation due to worsening pulmonary arterial hypertension, start of prostacyclin therapy or septostomy. The placebo group in 352 was significantly worse at week 16 compared to the bosentan groups. In 351, there were 3 placebo and 0 bosentan patients who deteriorated during the 12 week study.

Changes in Borg dyspnea index measures the levels of perceived exertion. In both studies, there were (small) improvements in the Borg scale in the bosentan groups (ranging from -0.1 to -0.6) compared to a worsening in the placebo groups (ranging from +0.3 to +1.36)

Changes in WHO functional class showed that more bosentan patients improved in their functional class compared to placebo patients.

Need for increased therapy for PAH occurred less often in the bosentan groups compared to placebo.

### **Risks**

The safety of oral bosentan has been tested in just over 1000 patients/subjects (includes second efficacy trial and clinical pharmacology trials). The indication for essential hypertension was discontinued for safety reasons.

### **Mortality**

The combined death rates for patients with PAH who participated in studies 351 and 352 were 2.4% for bosentan (4/165) and 2.5% for placebo (2/80).

### **Liver toxicity (black box warning)**

Approximately 10% to 11% of patients who took bosentan during the clinical program experienced increases in ALT or AST at least 3 times upper limit of normal and 4% had values greater than 8 times upper limit of normal. One patient had an elevated ALT that was 73 times higher than his baseline value. It appears that the higher the dose and the longer a patient takes any dose, the higher the risk of having an elevated LFT. Some, but not all patients with elevated LFTs also reported symptoms of abdominal pain, fever, fatigue, flu-like syndrome.

There are reports of patients with elevated bilirubin as well as two reports of jaundice<sup>1</sup> plus an additional report from a still blinded CHF trial (ENABLE).

Understanding that there is only a small population from which to draw conclusions, there is no indication at this time that the increase in liver enzymes will not be reversible with discontinuation of bosentan, at least in the majority of patients. There is no indication that bosentan was tied to any death (with the possible exception of REACH study in CHF patients that had an increase in deaths in the fast titration group) and there were no reports of liver failure or need for liver transplant.

In addition to patients being discontinued from bosentan for rising LFTs, patients complaining of fever and/or abdominal pain should be discontinued as well before more aggressive tactics (exploratory laparotomy, for example) are taken.

The protocols routinely excluded patients with AST/ALT > 3 times upper limit of normal and this should remain a contraindication.

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<sup>1</sup> patient 110 10037 in study AC 052 352 (see summary of efficacy) and 20060 0084 in study RO15464

### **Drug interactions with CYP3A4 inhibitors (black box warning)**

Medications whose concomitant use with bosentan is to be contraindicated include cyclosporin (bosentan concentration increased 30 fold) and ketoconazole.

### **Anemia**

There is a dose related mean decrease in hemoglobin in patients taking bosentan for more than 12 weeks. About 3% of patients reported serious anemia requiring withdrawal and/or transfusion. There was evidence in some, but not all, of these patients of blood loss that would account for such a drop in hb/hct. The one case of bone marrow biopsy<sup>2</sup> reported as normal is reassuring. Reticulocyte count<sup>3</sup> and erythropoietin levels were not measure. The sponsor's explanation that this is all the result of hemodilution seems unlikely.

There is no indication that there is irreversible harm done to patients who develop anemia when taking bosentan. Thus far, it appears that by stopping bosentan when patients show an unacceptable drop in hemoglobin/hematocrit results in patients returning to baseline levels. The protocols routinely excluded patients with hemoglobin and/or hematocrit <30% below normal limits.

### **Other adverse events**

Adverse events that were reported by at least 8 bosentan patients and reported by at least 1% more in the bosentan group compared to placebo include flushing, edema, headache, pruritus, angina, palpitations, and dry mouth. Although there was no evidence that bosentan is associated with hypotension, the protocols routinely exclude patients with systolic blood pressure < 85 mmHg.

Although there was one report of torsades de pointes, there is no indication that bosentan affects the electrical activity in the heart.

### **Other drug interactions**

Bosentan can be expected to decrease the concentrations (and may be the effect) of CYP3A4 and CYP2C9 substrates.

Other drugs that the sponsor prohibited study patients from taking include glibenclamide, encainide, flecainide, disopyramide, propafenone, moricizine, pinacidil, minoxidil and oral positive inotropic agents other than digitalis.

Patients receiving warfarin and bosentan must be monitored for decreases in prothrombin time. There are no safety data supporting the concomitant use of bosentan and prostacyclin therapy.

### **Conclusion**

Bosentan should be approved for improving walking distance in patients with WHO functional class III or IV, who are not responding adequately to conventional therapy, and are not taking Flolan. Because of the toxic effects on the liver and the serious drug-drug interactions, it is recommended that a patient registry with education for physicians who treat patients with PAH be implemented prior to the marketing of bosentan.

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<sup>2</sup> patient 18202/9032

<sup>3</sup> sponsor reports that in the ongoing ENABLE trials, mean reticulocyte count decreased by  $6.4 \times 10^9/l$  in the 285 patients with baseline and on treatment measurements, and the 26 patients with markedly decreased hemoglobin also had a decrease in mean reticulocyte count (fax dated 6-26-01).